DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Alan Minsk, Esq.
David Hoffman, Esq.
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1201 West Peachtree Street
2800 One Atlantic Center
Atlanta, Georgia 30309-3450

Re: Docket Nos. 2004P-0365/CP1 and PSA1

Dear Messrs. Minsk and Hoffman:

This letter responds to your petition dated August 13, 2004,[1] submitted on behalf of Shire US, Inc. (Shire), asking the Food and Drug Administration (FDA) to (1) refrain from approving any abbreviated new drug application (ANDA) for generic Agrylin (anagrelide hydrochloride) capsules that fails to include monitoring of the active metabolite 3-hydroxy anagrelide (3-HA) in bioequivalence testing to ensure that exposure to the metabolite is similar to that with Agrylin, and (2) require an ANDA applicant for anagrelide hydrochloride capsules to evaluate bioequivalence by monitoring the active metabolite under both fed and fasting conditions because it appears that food affects a patient's exposure to the parent drug and active metabolite in different ways.

This letter also responds to your petition for stay of action (PSA) dated September 2, 2004, submitted on behalf of Shire, asking FDA to stay the approval of any ANDA for anagrelide hydrochloride capsules until the Agency has reviewed and responded to your citizen petition.[2] For the reasons that follow, the petition and the PSA are denied.

I. Background

Agrylin is a prescription drug product indicated for the treatment of patients with thrombocythemia (a condition characterized by elevated blood platelets) secondary to myleproliferative disorders. Agrylin is used to reduce elevated platelet counts and the risk of thrombosis. Agrylin is also indicated for the amelioration of associated symptoms, including thrombo-hemorrhagic events.

[1] You submitted the petition approximately one month before your orphan drug exclusivity (to which pediatric exclusivity then attached) expired on September 14, 2004. Although you provide some historical context to frame the timing of your submission, we note that most of the studies you relied on were at least two years old at the time of submission —the earliest being 1981.

[2] FDA also received and considered comments submitted by Mylan Pharmaceuticals, Inc., dated September 8, 2004, and comments submitted by Barr Laboratories, Inc., dated October 20, 2004.

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FDA has designated Agrylin (NDA 20-333) as the reference listed drug for anagrelide hydrochloride capsules.

Agrylin capsules are available in 0.5 milligram (mg) and 1 mg strengths. Following administration, anagrelide is extensively metabolized in humans to two major metabolites: 3-hydroxy anagrelide (also known as SPD604, BCH24426, or 3-HA) and RL603.

II. Statutory and Regulatory Standards

The Federal Food, Drug, and Cosmetic Act (the Act) generally requires an ANDA applicant to provide, among other things, information to show that the generic drug[3] is bioequivalent[4] to the reference listed drug (21 U.S.C. 355 (j)(2)(A)(iv)). FDA must approve the ANDA unless the information submitted in the ANDA is insufficient to show that the generic drug is bioequivalent to the reference listed drug (21 U.S.C. 355(j)(4)(F)).

FDA's regulation at 21 CFR 320.24 lists the in vivo and in vitro methods of determining bioavailability or bioequivalence for a drug product in descending order of accuracy, sensitivity, and reproducibility. Because anagrelide is the active moiety and can be readily measured in plasma, § 320.24(b)(1)(i) provides that the most appropriate method for testing the bioavailability or bioequivalence of the drug product is "[a]n in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time."[5]

Section 320.24(b)(1)(i) states that "this approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for system distribution within the body." Accordingly, this approach applies to ANDA applicants seeking approval of anagrelide hydrochloride capsules.

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[3] For brevity the term "generic drug" refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[4] Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if "(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug." See 21 U.S.C. 355(j)(8)(B).

[5] As you request (Petition at 7), ANDA applicants for anagrelide are expected to conduct bioequivalence studies using in vivo testing.

III. FDA's Guidance for Industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*

FDA's guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (BA/BE guidance) (p. 17-18) provides, among other things, recommendations concerning the measurement of either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolite(s). For bioequivalence studies, the BA/BE guidance (p. 18) generally recommends measurement of only the parent drug (the moiety released from the dosage form), rather than the metabolite. The basis for this recommendation is that the "concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination" (BA/BE guidance, p. 18).

The BA/BE guidance describes two situations when the above general recommendation (i.e., measuring the parent drug only) does not apply. The first situation is when the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The parent drug anagrelide can be reliably measured in plasma, and thus this case does not apply here. The second situation is described on page 18 of the BA/BE guidance:

> A metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not have to be measured. We recommend that the parent drug measured in these BE studies be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

We cannot conclude based on currently available scientific evidence that (1) 3-HA is formed as a result of presystemic metabolism, and (2) 3-HA contributes meaningfully to the safety and/or efficacy of the drug product. As discussed below, we do not currently expect ANDA applicants for anagrelide hydrochloride capsules to measure 3-HA in bioequivalence testing.

IV. Metabolism of 3-HA

You assert that 3-HA is generated during presystemic metabolism and that this "means that a patient's exposure to the active metabolite could be affected by

changes in the drug formulation" (Petition at 7). You state that "a drug's formulation will only influence plasma exposure to an active metabolite when the metabolite is formed presystemically" (Petition at 9). You also state that the Agency's BA/BE guidance recommends assessing metabolite exposure in a bioequivalence study "only when it is determined that the metabolite is formed presystemically" (Petition at 9).

Your argument that 3-HA is formed presystemically is a rather tenuous one that is based on various in vitro studies as well as theories about presystemic metabolism, first pass effect in the liver,[6] and how to calculate the bioavailability of an oral dosage form.[7]

Bioavailability is best determined using an intravenous formulation. A drug administered intravenously is considered 100 percent bioavailable because 100 percent of the dose reaches the systemic circulation. The absolute bioavailability of a drug that is orally administered is usually equal to or less than 100 percent. Absolute oral bioavailability (the percentage of the dose that reaches the systemic circulation) is determined by comparing the area under the curve (AUC) following oral administration of a dose of the drug with the AUC of the same dose of the drug administered intravenously.

You have not directly measured the absolute oral bioavailability of anagrelide because you have not, as you concede, developed an intravenous form of the drug with which to make the comparison to the oral form (Petition at 9). Instead, you claim that certain equations "can be used to estimate anagrelide's oral bioavailability" (Petition at 11). Applying these equations to calculate bioavailability in 18 patients with essential thrombocythemia, you state that the results indicate that the mean oral bioavailability of anagrelide is 52.6 percent, plus or minus 12.5 percent. You claim that your estimate of oral bioavailability means that up to 48 percent of the oral dose could be metabolized during the drug's initial passage through the liver (Petition at 11).

We cannot conclude that your offered estimate and theory constitute sufficient evidence to ask ANDA applicants for anagrelide hydrochloride capsules to monitor 3-HA in bioequivalence testing. As you acknowledge, the equations you used assume that 100 percent of the dose of anagrelide is absorbed and that 100 percent of clearance of the drug is by the liver. You have not provided sufficient evidence for either of these assumptions.

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[6] First pass effect in the liver is a form of presystemic metabolism.

[7] We note that your petition does not make your argument in a straightforward fashion and that some of the theories you rely on (which are not persuasive for the reasons set forth above) and the evidence for them are not clearly presented in the petition (although you characterize the information as summaries of "Shire data on file").

As evidence for "near quantitative" absorption[8] of anagrelide, you rely on data from two radio-labeled human studies. One study reported that 78.34 percent, plus or minus 1.5 percent, of the 1 mg dose of anagrelide was recovered in urine, and that recovery in feces averaged 20.2 percent, plus or minus 3.5 percent. The other study reported that 71.8 percent, plus or minus 7 percent, of anagrelide was recovered in urine, and 10.2 percent, plus or minus 5.8 percent, was recovered in feces. Based on these studies, you conclude that anagrelide is rapidly absorbed and undergoes extensive metabolism. By averaging the means from these studies, you suggest that about 75 percent of the dose appears to be absorbed following oral administration.

The equations you used to estimate the oral bioavailability of anagrelide assume that 100 percent of the dose is absorbed, yet your radio-labeled studies suggest that only 71 to 75 percent of the dose is absorbed. Furthermore, the sample size in both studies was too small to be reliable. The first study initially included only five healthy subjects. There was incomplete urine collection from one subject at 8 to 12 hours, and therefore, complete data were available for only four subjects. In the second study, the sample size was only five.

You believe there is evidence that anagrelide is quantitatively absorbed from and is not chemically degraded within the gastrointestinal tract (Petition at 9).[9] From this, you conclude that anagrelide's oral bioavailability is determined only by hepatic presystemic metabolism (Petition at 9). Although you provide no further explanation, presumably the theory behind your conclusion is that if there is no degradation in the gastrointestinal tract, the total fraction of the anagrelide dose passing through the intestinal wall is absorbed unchanged; this fraction then goes

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[8] We assume that "near quantitative" absorption, means "almost complete" absorption.

[9] Attachment H to the petition, page 7, discusses an in vitro study performed with fecal suspensions to investigate the possibility of in vitro biotransformation of radio-labeled anagrelide by human gut microflora. The study reported that less than 10 percent of the drug had apparently disappeared. Based on these results, you concluded that there was no evidence for gut luminal metabolism of anagrelide.

On page 8 of Attachment H, you refer to another study using human intestinal microsomes. You state that after 45 minutes of incubation, 86.4 percent of anagrelide was not metabolized.

You provided only summary conclusions about these studies, and characterized the information as "summary of Shire data on file" (Attachment H, p. 1). In any event, we note that in vitro studies in general, especially when they do not rely on validated, standardized methods, are not always reliable and may be poor predictors of in vivo activity. In addition, the results of in vitro studies can be highly influenced by experimental conditions.

You also state that CYP1A2 is likely to be involved in the metabolism of anagrelide, and this isozyme is not present in the gut wall. Even if your theory that this particular enzyme is not present in the gut wall is correct, it does not establish that 3-HA is presystemically formed in the gut wall because your theory does not preclude the possibility that other enzymes may be involved in the metabolism of anagrelide.

to the liver, where a fraction of the dose is lost before reaching the systemic circulation—meaning that the bioavailability of anagrelide is determined solely by hepatic first pass.

You supply evidence of hepatic clearance to support this conclusion. Specifically, you state that hepatic impairment affects the pharmacokinetics of anagrelide by causing an 8-fold increase in AUC (Petition at 10). The fact that hepatic impairment affects the pharmacokinetics of anagrelide does not support your argument that anagrelide is presystemically metabolized. An increase in AUC with hepatic impairment only shows that the contribution of hepatic metabolism may have decreased in this patient population; it does not necessarily indicate presystemic metabolism. In fact, you acknowledge that part of the 8-fold increase in AUC "could be related to the 2.2-fold increase in half-life and a possible reduction in volume of distribution. . . ." (Petition at 10). Furthermore, it is expected that a drug metabolized in the liver would have reduced clearance in hepatically impaired subjects; it is not evidence of a significant first pass effect.

You also state that pharmacokinetic studies in 38 healthy subjects "have indirectly generated information on anagrelide's presystemic metabolism" (Petition at 9). In one study, the Tmax (mean ± relative standard deviation) for anagrelide was 1.3 hours ± 53.8 percent and the Tmax for 3-HA was 1.28 hours ± 58.1 percent (Attachment H, p. 5). You argue that "the rate of formation of [3-HA] appeared to proceed in parallel with the absorption of the drug, suggesting that the metabolite's formation was effected [sic] by first-pass metabolism of anagrelide" (Petition at 9). This information is not persuasive evidence of first-pass metabolism. The apparent rate of formation of a metabolite is affected by several factors, including the actual rate of metabolite formation, the rate of renal excretion of the metabolite, sampling time points, and the absorption rate of the parent drug. Parallel formation of the metabolite is not direct evidence of significant first pass metabolism.[10]

You have not directly measured the oral bioavailability of anagrelide, and the indirect evidence you have presented fails to adequately demonstrate that anagrelide is presystemically metabolized to any significant extent. Therefore, you have not shown that anagrelide falls within the circumstances described in the BA/BE guidance under which FDA recommends measurement of a metabolite. As a result, FDA does not need to ask ANDA applicants to measure 3-HA in bioequivalence testing of anagrelide hydrochloride capsules based on the BA/BE guidance.

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[10] Jackson A, G Robbie G, P Marroum, 2004, Metabolites and Bioequivalence: Past and Present. Clin Pharmacokinet, 43(10):655-672.

V. Claims that 3-HA Contributes Meaningfully to the Safety and/or Efficacy of Agrylin

We have already concluded above that the currently available scientific evidence (including that you submitted) does not show that 3-HA is formed as a result of presystemic metabolism to any significant extent. Even assuming that you could show that 3-HA is formed as a result of presystemic metabolism, as discussed below, there is insufficient scientific evidence to conclude that 3-HA makes a meaningful contribution to the safety and/or efficacy of Agrylin. Accordingly, we would still not expect generic applicants to measure 3-HA in bioequivalence testing.

A. Inhibition of Megakaryocyte Production

You claim that in vitro studies demonstrated that 3-HA was comparable to the parent molecule anagrelide in its platelet lowering activity (Petition at 8). This claim is based on your assumption that the mechanism by which anagrelide reduces platelet count is by inhibiting megakaryocyte maturation. In effect, you are arguing that 3-HA contributes to the efficacy of Agrylin.

We agree that, in an in vitro assay, 3-HA produced effects similar to anagrelide on megakaryocyte glycoprotein IIIa expression and megakaryocyte cell size. However, this fact does not demonstrate that 3-HA makes a significant contribution to the efficacy of Agrylin in humans. First, it has not been established that Agrylin works by inhibiting megakaryocyte maturation. In fact, the labeling for Agrylin states: "The mechanism by which anagrelide reduces blood platelet count is still under investigation. . . . Studies in patients support a hypothesis of dose-related reduction in platelet production resulting from a decrease in megakaryocyte hypermaturation."

Thus, the labeling of the product states that it is only a hypothesis that the mechanism by which anagrelide reduces platelet count is by inhibiting megakaryocyte maturation.

Second, there is no validated model to demonstrate that these in vitro results predict the clinical performance of Agrylin in humans. The best way to determine the effect of a metabolite is to administer both the metabolite and the parent molecule separately to human subjects in a well-controlled clinical trial. You have not conducted such a clinical trial. Such a trial would need to show that subjects administered 3-HA showed a clinically significant reduction in platelet count. In sum, you have not demonstrated that 3-HA contributes to the efficacy of Agrylin.

B. Phosphodiesterase III Inhibition

You claim that 3-HA is a highly potent phosphodiesterase III (PDE III) inhibitor (Petition at 4, 8). You state that in vitro studies show that 3-HA is nearly 40 times more potent than anagrelide as a PDE III inhibitor (Petition at 8). You state that anagrelide's cardiostimulant activity, which manifests in side effects such as tachycardia and palpitations, is likely due to 3-HA (Petition at 8). You assert that this purported connection between 3-HA and PDE III is evidence that 3-HA contributes significantly to the pharmacological activity of Agrylin (Petition at 8). It would seem that you are claiming that 3-HA affects the safety of Agrylin, and that bioequivalence testing should measure 3-HA "to provide assurance that there is not an unexpected exposure to this cardiostimulant metabolite. . . ." (Petition at 4).

You conducted several in vitro studies concerning PDE III inhibition. Some studies measured 3-HA and others measured anagrelide. Inconsistent results concerning the potency of 3-HA as a PDE III inhibitor were obtained in these studies. This inconsistency calls into question your assertion that 3-HA is 40 times more potent than anagrelide in PDE III inhibition.

You also state that a cardiovascular pharmacology study on 3-HA in the anesthetized dog model demonstrated that 3-HA was "10 to 20 times more potent than the reference positive inotrope, milrinone, which [3-HA] closely resembled with respect to its inotropic, chronotropic, and vasodilatory activity" (Petition at 8). You state that milrinone is a cardiostimulant used clinically in the treatment of congestive heart failure that "requires careful monitoring in view of its profound effects on the cardiovascular system and consequential safety concerns" (Petition at 4).

This comparison of 3-HA to milrinone is not relevant. It is the potency of anagrelide and 3-HA as PDE III inhibitors that is the relevant comparison. Furthermore, previous studies have found that, following anagrelide administration, intra-arterial blood pressure was reduced and heart rate increased in a variety of animal species, including rats, dogs, and ferrets. The dog study you submitted only suggests that 3-HA may have an effect similar to that of anagrelide. We agree that it is likely that PDE III inhibition is responsible for the cardiovascular effects that are sometimes observed after administration of Agrylin. However, you have not performed the properly designed studies that would establish to what extent PDE III inhibition is due to the parent drug anagrelide and to what extent it is due to the metabolite 3-HA. The in vitro studies and the dog study you cite do not provide persuasive evidence to reasonably conclude that 3-HA has an effect on the safety of Agrylin.

C. PK/PD Study in Patients

You conducted a steady-state pharmacokinetic and pharmacodynamic study (PK/PD study) in 17 pediatric patients who were compared with 18 adult patients. The majority of patients in the study had received various daily doses of anagrelide for an average of 2 years before entering the study. You report that the plasma exposure to 3-HA was more than twice that of the anagrelide (Petition at 3, 8, 13). You conclude that the greater plasma exposure to 3-HA indicates that 3-HA is a major contributor to the efficacy and safety of Agrylin (Petition at 3).

Using a log-linear model, you also attempted to correlate the Cmax values for anagrelide and for 3-HA with changes in individual platelet counts at steady state from those at baseline. Also using a log-linear model, you attempted to correlate the Cmax values for anagrelide and for 3-HA with maximal change in heart rate.

The PK/PD study showed that in the pediatric/adolescent subjects, the mean Cmax of 3-HA was 2.9 times higher than the value for anagrelide (5.5 nanograms (ng)/milliliters (mL) and 1.9 ng/mL, respectively). In the adolescent/adult subjects, the mean Cmax value of 3-HA was similar to that of anagrelide (4.5ng/mL and 3.1 ng/mL). Because the correlation between changes in platelet count and log plasma concentrations appears to be stronger for 3-HA than for anagrelide, you conclude that 3-HA is an active metabolite that contributes to the safety and effectiveness of the drug product.

FDA does not agree with the conclusion you draw from this study, based as it is on unsubstantiated theory. The correlation approach you take is too simplistic to show that 3-HA is pharmacologically active. You have not demonstrated that it is clinically significant that plasma levels of 3-HA were two times higher than levels of anagrelide. The differences in Cmax you observed between anagrelide and 3-HA are not meaningful because the effect of 3-HA cannot be separated from the effect of the parent drug. To separate the effects of the parent and the metabolite, we would expect each to be administered separately to human subjects in a clinical trial. In sum, you have not demonstrated that 3-HA contributes to the safety and/or efficacy of Agrylin.

VI. The Need for a Food Effect Study

You conducted a pharmacokinetic study in normal subjects to investigate the effect of food on the disposition of the parent drug and 3-HA. You state that the study showed that food affected the parent drug and 3-HA differently. The study showed that in the presence of food the Cmax of anagrelide decreased approximately 14 percent and the AUC increased approximately 20 percent, while the Cmax of 3-HA decreased approximately 30 percent, and there was no change in AUC. You conclude that these reported changes with food indicate that the relationship between anagrelide and 3-HA, with respect to their exposure-time

profiles, is not straightforward and that bioequivalence studies on anagrelide should include monitoring of 3-HA in both fed and fasting states (Petition at 12).

To justify measuring 3-HA in a fed bioequivalence study, we would expect there to be evidence to show that 3-HA is formed by presystemic metabolism and that it contributes meaningfully to the safety and/or efficacy of Agrylin. For the reasons discussed above in sections IV and V, you have not made this showing. Therefore, FDA currently does not intend to ask ANDA applicants for generic versions of Agrylin to measure 3-HA in bioequivalence studies, either fasting or fed.

We currently do intend, however, to ask ANDA applicants to measure the parent drug, anagrelide, in both fasting and fed states.[11] Our guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (p. 3-4) recommends that ANDA applicants conduct a bioequivalence study under fed conditions (in addition to fasting conditions) for all orally administered immediate-release drug products unless the following exceptions apply:

> (1) When both test product and RLD [reference listed drug] are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability . . ., or
> (2) When the DOSAGE AND ADMINISTRATION section of the RLD labeling states that the product should be taken only on an empty stomach, or
> (3) When the RLD labeling does not make any statements about the effect of food on absorption or administration.

None of these exceptions apply, and therefore we intend to ask ANDA applicants to measure the parent drug, anagrelide, in both fasting and fed states.

VII. Petition for Stay of Action

You ask FDA to stay the approval of any ANDA for anagrelide hydrochloride capsules until we have reviewed and responded to your citizen petition.

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action:

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[11] You have not asked FDA to issue a product-specific guidance concerning bioequivalence studies for anagrelide hydrochloride capsules. However, you point out that in the past FDA has sometimes issued such guidances for compounds with active metabolites (Petition at 13). Your point is only that such guidances "emphasize the importance that FDA attaches to active metabolite monitoring" (Petition at 13). We currently do not intend to issue a guidance concerning bioequivalence testing for anagrelide hydrochloride capsules. The BA/BE guidance provides ANDA applicants for anagrelide hydrochloride capsules with appropriate bioequivalence testing recommendations.

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
> (1) The petitioner will otherwise suffer irreparable injury.
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
> (4) The delay resulting from the stay is not outweighed by public health or other public interests.

FDA will grant a stay only when all the provisions set forth in § 10.35(e)(1)-(4) have been satisfied. We need not address your claim that your case is not frivolous and is being pursued in good faith and that you would otherwise suffer irreparable injury because we conclude that you have not demonstrated sound public policy grounds for a stay. Furthermore, we conclude that the potential delay resulting from the stay is outweighed by public health or other public interests.

You assert that your request for stay is supported by sound public policy grounds. You state that the stay "merely request[s] FDA to ensure that any generic version of Agrylin is bioequivalent to Agrylin. FDA's bioequivalence regulations are designed to encourage the sale of generic drug products that have proven themselves to be as safe and effective as the reference listed drug" (PSA at 3). For this reason, you argue that your request for stay "is supported by the public health grounds that serve as the foundation of FDA's bioequivalence regulations" (PSA at 3).

As discussed throughout this response, we have concluded that you have not supported your requests that ANDA applicants for anagrelide hydrochloride capsules be required to monitor or measure 3-HA in bioequivalence testing or monitor 3-HA in both fed and fasting states. We also conclude that any generic anagrelide hydrochloride capsules approved by FDA will be as safe and effective as Agrylin. Therefore, your request for stay is not supported by public health grounds.

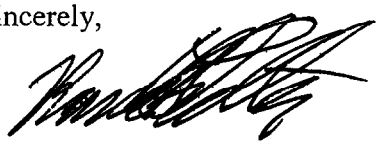
You assert that your request for stay is not outweighed by public health or other public interests. We disagree. Approval of ANDAs for generic drug products is one of the Agency's important public health initiatives. The dual purpose of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law No. 98-417, 98 Stat. 1585), which established the ANDA process, was to expedite the availability of safe, effective, and less expensive generic versions of approved drugs while simultaneously encouraging the costly research and development

efforts that lead to the discovery of therapeutically important new drugs. Consequently, it would not be in the public interest for us to stay approval of any ANDA for anagrelide hydrochloride capsules that meets the statutory and regulatory requirements for approval. We conclude that the delay resulting from the stay of such ANDAs would be outweighed by the public health interests in approving ANDAs that meet the statutory standards for approval.

VIII. Conclusion

For the reasons discussed above, your petition is denied. Based on the currently available scientific evidence, FDA does not intend to ask ANDA applicants for anagrelide hydrochloride capsules to monitor or measure 3-HA in bioequivalence testing. The Agency also denies your request that ANDA applicants monitor 3-HA in both fed and fasting states because the currently available scientific evidence does not warrant such monitoring. Finally, as discussed above, your petition for stay is denied.

Sincerely,



Randall W. Lutter, Ph.D.
Acting Associate Commissioner
for Policy and Planning